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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/155,708	04/05/99	FARRAR G	MUR-75

HM22/1005
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EXAMINER	
EPPS,J	
ART UNIT	**PAPER NUMBER**
1635	17

DATE MAILED: 10/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/155,708	Applicant(s) FARRAR ET AL.	
	Examiner Janet L. Epps	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 12-44 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 12-44 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

WILLIAM N. PRUL
PATENT ANALYST

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. Claims 12-44, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record in the rejection of claims 1-3 and 11under 35 USC § 112, first paragraph, set forth in the Official Action mailed 2-13-01.

Applicant's arguments filed 7-13-01 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification fully enables new claims 12-44 since Applicants gives detailed examples in their specification which provide steps for practicing the invention. Furthermore Applicants argue that "there is no reason to believe that Applicant's method for designing the suppression of a mutant allele of a gene and providing a replacement allele, would not work *in vivo* for suppressing a gene, given the state of the art of gene therapy, antisense and ribozymes." The Examiner agrees that Applicants provide a number of examples demonstrating mutation specific cleavage of a mutant mRNA transcript by the use of a ribozyme. However, Applicant's provide only a non-cellular *in vitro* assay to demonstrate the efficacy of ribozyme suppressors to cleave the transcript of a mutant allele. It is unclear how this *in vitro* assay is to be used to predict the behavior of Applicant's ribozyme suppressors *in vivo* when used in their claimed therapeutic method for treating a genetic disease. As stated in the prior Official Action, due to a significant level of unpredictability regarding the

behavior of nucleic acid base therapeutics, "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate," according to Crooke (1998).

Furthermore, Applicants provide a series of references to support the assertion that ribozyme art was no unpredictable at the time of filing of the instant Application. For example, Applicants provide the Lieber et al. reference to support the notion that ribozymes could be designed using 2° structure modeling and testing in vitro) which then cleaved RNA in vivo. Contrary to Applicant's description of the Lieber et al. reference, Lieber et al. provide only cell culture studies demonstrating the efficacy of their ribozymes. Furthermore, in regards to the references of Lieber et al., Kay, US Patent Nos. 5,246,921, and 5,834,440, submitted to provide the state of the art of the ribozyme art at the time of filing, it is noted that the disclosures of these references do not provide any guidance as to how to use the full scope of the claimed invention, particularly for treating a genetic disease in a subject comprising gene replacement in combination with an mutant allele specific suppressor. Moreover, the facts that are relied upon in the above references are different from those discussed in the instant application. Applicants do not discuss use of the same compounds or methods described by the instant references. There is no evidence that the compounds or methods discussed in Lieber et al., Kay, US Patent Nos. 5,246,921, or 5,834,440 would supplement the instant specification to provide sufficient guidance and/or instruction that would allow one of skill in the art to practice the full scope of the claimed invention without undue experimentation. The cited references do not overcome the deficiencies of the instant specification such that one of skill in the art would be able to treat any genetic disorder in a human merely by following the disclosure of the cited references and the

specification as filed. The cited references do not even make mention of the full range of inhibitors encompassed by the instant method, for example the use of peptides, peptide nucleic acid, antibodies, and triplex oligonucleotides.

It is noted that Applicants have not addressed the issues of unpredictability noted in either Crooke (1998) or Branch (1998) (both published after the filing and/or publication dates of the references cited by Applicants) set forth in the prior Official Action. Moreover, Applicant's response is incomplete to the extent that Applicants do not address the issue of unpredictability in the gene therapy art as described by Gómez-Navarro et al. (1999) and Marshall (1995), Applicants have only described the issues regarding antisense and ribozyme therapies.

In summary Applicants provide prior art citation to provide enablement for the use of ribozymes and oligonucleotides as suppression effectors, however the use of suppression effectors is only one aspect of the claimed invention. To practice the full scope of the claimed invention requires the identification of mutant alleles associated with a genetic disease, determination of the structure of those mutant alleles, providing a normal replacement copy of the mutant allele into a cell, inactivating the mutant allele, and expressing the replacement copy in a sufficient amount in order to produce a therapeutic effect in an individual. As stated in the prior official action, there are numerous factors that complicate therapeutic methods comprising gene delivery *in vivo* which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the

mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated. Applicants have not addressed these issues as set forth in the prior Official Action.

Therefore, as stated previously, the specification as filed does not describe the full scope of the claimed invention, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the delivery of therapeutic genes *in vivo,* the behavior of antisense oligonucleotides *in vivo* and further with providing a beneficial effect in a patient, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single endogenous gene is suppressed and replaced and the desired secondary effect (treatment leading to the amelioration of conditions associated with the expression of said endogenous gene) is obtained. The specification as filed does not provide any guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Applicant's arguments do not take the place of evidence. The instant claims are rejected for the same reasons set forth in the rejection of claims 1-3 and 11 under 35 USC § 112, first paragraph, set forth in the prior Official Action.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on Mondays through Friday, 9:00AM to 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps
Examiner
Art Unit 1635

JLE
October 2, 2001

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600